THE RELATION BETWEEN STRUCTURE AND ODOR IN DERIVATIVES OF BETA-PHENYLETHYL ALCOHOL SOME NEW BETA-PHENYLACRYLIC ACIDS.

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DISSERTATION.

Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
in the Faculty of Pure Science,
Columbia University.

BY

EDMUND H. HAMANN, A.B., A.M.

NEW YORK CITY
1927

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THE RELATION BETWEEN STRUCTURE AND ODOR IN DERIVATIVES OF BETA-PHENYLETHYL ALCOHOL SOME NEW BETA-PHENYLACRYLIC ACIDS.

ABSTRACT

The study and preparation of derivatives of β-phenylethyl alcohol was undertaken with a view to their possible value as perfume constituents and to gain further information as to the relation between structure and odor.

Since β-phenylethyl alcohol itself is obtained from nature and manufactured for use in perfumes, and since phenolic ethers are found in many essential oils and are manufactured and used extensively in the perfume industry, a combination of these two types seemed worthy of investigation.

In the first types investigated the ether and alcohol radicles were in ortho position to each other and a methyl radicle was para to the ether radicle. These compounds had faint odors the intensity of which decreased with the lengthening of the ether chain. The quality of odor remained unchanged and likewise its nature was always phenolic. Any similarity to the odor of β-phenylethyl alcohol was removed.

When the methyl group was removed there was a marked increase in odor intensity, the nature and quality remaining the same.

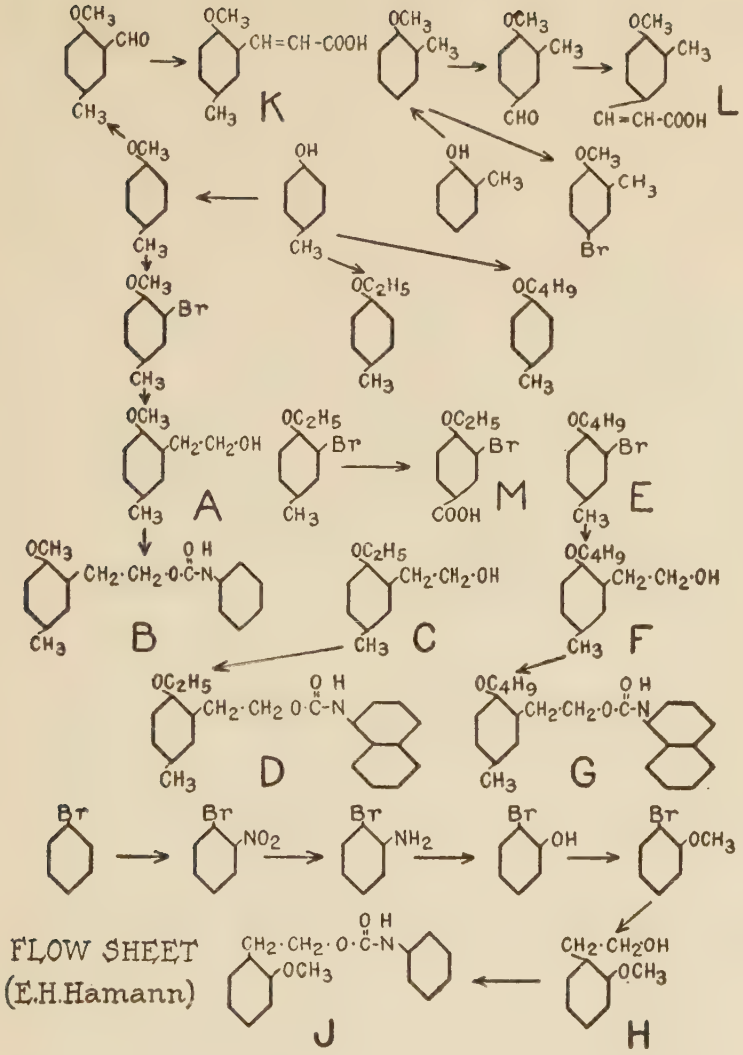
These results supported the generally accepted view that increase in the length of carbon chains diminished odor intensity. The marked effect of the removal of the methyl group supported the theory that odor could not be entirely attributed to odorous groups, osmophores, but also depended upon molecular structure; so that while in long-chain, aliphatic compounds the influence of an additional methyl group may only be slight, it was much greater when introduced into an aro-

matic neucleus because the molecular symmetry was more disturbed.

With a view to comparing the corresponding cinnamyl alcohols in the same manner two substituted β-phenylacrylic acids were prepared. Due to difficulties unforseen, this work was carried no further.

In the course of this research the following new compounds have been prepared.

A. β(3-methyl-6-methoxyphenyl) ethanol
B. β(3-methyl-6-methoxy-phenylethyl) phenylcarbamate
C. β(3-methyl-6-ethoxyphenyl) ethanol
D. β(3-methyl-6-ethoxy-phenylethyl)αnaphthylcarbamate
E. 2-brom-4-methylphenyl butyl ether
F. β(3-methyl-6-butoxyphenyl) ethanol
G. β(3-methyl-6-butoxy-phenylethyl)αnaphthylcarbamate
H. β(2-methoxyphenyl) ethanol
J. β(2-methoxy-phenylethyl) phenylcarbamate
K. β(3-methyl-6-methoxyphenyl) acrylic acid
L. β(3-methyl-4-methoxyphenyl) acrylic acid
M. 3-brom-4-ethoxy benzoic acid.


OCH3
CHO
CH3
K
CH=CH-COOH
L
CH=CH-COOH
OH
Br
OC2H5
OC4H9
A
M
E
B
C
F
D
G
NO2
NH2
OH
J
H
FLOW SHEET
(E.H.Hamann)

INTRODUCTION

On review of the literature it was seen that little work had been done on derivatives of β-phenylethyl alcohol with a view to establishing any relation between structure and odor. The work of Grignard [31, 37], Bert [54] and others was not carried out for this purpose as much as it was to establish new methods of synthesis. v. Braun[43, 45] seemed to be the only worker in the field of aromatic alcohols who had worked with this idea, but he was mainly interested in comparing the alcohols themselves and substitutions in the alcohol group, not on the ring.

Hydroxyl derivatives of aromatic alcohols have little or no odor. The hydroxy benzyl alcohols[4, 20, 5] were not described in regard to odor. Only the meta compound [5] was described as odorless. We may assume that the former two were odorless also. On the other hand the ortho methoxy and ethoxy benzyl alcohols possessed an agreeable aromatic odor.[9] Likewise, for derivatives of β-phenylethyl alcohol with a para hydroxyl group as in tyrosol there was no odor.[21] The para methoxy compound, however, was a substance with a clear anise-like odor.[31, 32, 37] β(3-methyl-4-methoxyphenyl) ethanol had a mild pleasant odor.[47]

That these compounds with a free hydroxyl group should be odorless was to be expected from their decreased volatility. By esterifying the hydroxyl they became liquid substances and more volatile, and gained in intensity. From these observations it seemed that ether groups would influence the odor of phenylethyl alcohol favorably, bearing in mind that odors, if mentioned, were of minor importance to the above workers, and also the difficulty in determining and describing an odor.

That the methyl group should have much influence was not expected. It was only used to keep the ideal configuration, the 1-2-4 type of substitution, which, as pointed out by Cohn,[52] is that most frequently found in natural and synthetic odorous substances. Of the monomethyl, ring-substituted phenylethyl alcohols o-methyl-β-phenylethyl alcohol was described as having a fairly strong, aromatic odor,[31, 37] p-methyl-β-phenylethyl alcohol a weak odor,[31, 37] and m-methyl-β-phenylethyl alcohol

an odor differing little from the unsubstituted alcohol.[45] It was therefore unexpected that the removal of the methyl radicle from β(3-methyl-6-methoxyphenyl) ethanol should cause such a marked change in odorous intensity. The methyl group was thus seen to be of much more influence when substituted in the nucleus than in the side chain.

DISCUSSION

Toluene was first selected as a starting material. The 2-4 dinitro derivative was prepared,[1] partially reduced,[1, 44] diazotised [34] and then replaced either by a hydroxyl group[30, 46] or by a halogen.[34] If it was replaced by an hydroxyl this was then esterified and the nitro group in the ortho position was reduced, diazotised and replaced by a halogen. If the para nitro was replaced by a halogen, the ortho nitro group was reduced, diazotised, hydrolysed and the resulting phenol esterified. But this method was found to be impractical, the yields being very poor, especially in the case of diazotizations followed by halogen or hydroxyl replacements, in which tars were formed.

To avoid these difficulties para cresol was used as starting material. The cresol used was that obtained from Eastman Co. labeled "practical," melting 32-34°.

With this material several methods for the introduction of one halogen were tried. An attempt to nitrate p-cresol directly to form 1-hydroxy-2-nitro-4-methyl benzene, according to the procedure given by Hofmann and Mueller,[7] was unsuccessful. Only the dinitro compound was obtained melting at 85°.[8] The bromination of the potassium salt of p-cresol, following the method of Schall and Dralle,[10] was tried but no monobrom p-cresol could be isolated. The dibrom compound was obtained melting at 48°.[11] The para cresol was then methylated and treated with phosphorous penta-bromide, as given by Authenrieth and Mühlinghaus[35] in the bromination of p-cresyl ethyl

ether. No bromine derivative was obtained. Therefore other means were looked for.

Claus and Jackson[19] brominated o-cresol directly in chloroform solution, using iron as a catalyst, and Zincke and Hedenstrom[36] using chloroform as solvent but without a catalyst. Later Meldrum and Shah [50] brominated o-cresyl methyl ether in acetic acid without a catalyst and obtained the monobrom compound. It therefore seemed best to brominate p-cresyl ethers directly, using chloroform as solvent. The use of iron as a catalyst had no influence on the number or position of the entering bromine, but was an aid in diminishing the time of reaction. The use of chloroform as a solvent could be dispensed with and the temperature seemed to be of little importance in the reaction. The brominations were usually carried out at 25-30° adding the bromine slowly enough so that the temperature did not rise above this point. This was done with methyl, ethyl and butyl p-cresyl ethers. The yields were 80-85%.

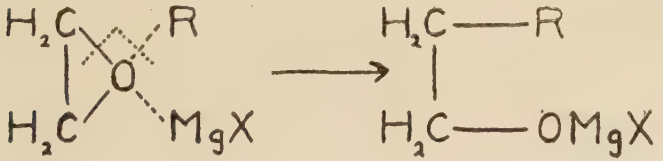
The ethers were prepared by dissolving sodium in 95% ethyl alcohol, adding the p-cresol, then the alkyl halide—usually the bromide, as was done by Authenrieth and Mühlinghaus[35] and Decker and Solonina[27] in preparing thymol ethyl ether.

From these monobrom ethers phenylethyl alcohol derivatives could be obtained by the Grignard reaction with ethylenechlorhydrin[31, 37] or ethylene oxide.[47, 48] If the first method had been used, two mols of the organo-magnesium halide had to be used to one of ethylene chlorhydrin, for the hydroxyl group would have first decomposed one mol before the second phase of the reaction occurred. Thus:

$$RMgX+Cl(CH_2)_2OH \rightarrow Cl(CH_2)_2OMgX+RH$$
$$Cl(CH_2)_2OMgX + RMgX \rightarrow R(CH_2)_2OMgX+MgXCl$$

The use of ethylene oxide, however, presented no difficulties. This was first used by Grignard [28] in preparing primary alcohols of the aliphatic series, and later this method was patented by Altwegg[47] for the preparation of phenylethyl alcohol and derivatives. The suggested mechanism of this reac-

tion consisted at first in the fixture of the organo-magnesium halide on the ethylene oxide forming the organo-magnesium etherate. Thus a complex was obtained which by action of heat underwent a transportation of the primary and secondary valences of the oxonium compound with the rupture of the ring.



On hydrolysis this product yielded a primary alcohol containing two atoms of carbon more than the original alkyl or aryl halide.

Higher temperatures than the boiling point of ether were necessary to complete the reaction, which was a rearrangement of the oxonium compound. This was done by adding a higher boiling solvent such as benzene or toluene, and distilling off the ether on a water bath, before decomposing the product with water. If this was not done the decomposition resulted in splitting off the ethylene oxide and hydrolysing the organo-magnesium halide to the hydrocarbon—in this case the cresol ether. In some cases, after preliminary heating to distill off the ether, this rearrangement was accompanied by enough heat so that the ether distilled without further heating. This seemed to be determined by the ratio of the amount of solvent used to the quantity of organo-magnesium-ethylene oxide addition product.

The alcohols were obtained after fractionation at reduced pressure, using a vacuum oil pump with which pressures of about one millimeter could be obtained. β(3-methyl-6-methoxyphenyl) ethanol was obtained as a thick liquid which solidified on standing and could be recrystallized from petroleum ether. β(3-methyl6-ethoxyphenyl)ethanol and β(3-methyl-6-butoxyphenyl)ethanol were viscous colorless liquids, the former of which crystallized on cooling with ice, but liquified

again at room temperature. The latter did not solidify in an ice and salt freezing mixture.

To further characterize these alcohols the phenylurethanes were prepared[25] and analysed. Only in the case of β(3-methyl-6-methoxy-phenyl)ethanol could a good analysis be obtained. This formed small, colorless needles. Phenylurethanes of the ethoxy and butoxy derivatives due to low melting points presented difficulties in crystallization, and separated out as oils from alcohol before they became solid. Therefore it seemed better to prepare the α-naphthylurethanes, using α-naphthyl isocyanate as done by Bickel and French.[62] These melted about 60° higher than the corresponding phenylurethanes and gave good analyses for carbon and hydrogen. They also formed small, colorless needles when crystallized from ligroin and dilute alcohol.

To prepare isomers of these alcohols ortho cresol (Eimer & Amend, "technical," b.p.188.5-189.5°) was taken as starting material. It was first esterified and then brominated. This product, 2-methyl-4-brom anisole, melted 68-68.5° cor. and not at 74° as stated by Meldrum and Shah[50]. They also stated that this compound crystallized with 1½ molecules of water of crystallization, but no loss in weight occurred when the compound was heated above 120°. Analyses for bromine, carbon and hydrogen agreed with the formula, C_8H_9OBr. The corresponding acid, 3-brom-6-methoxy benzoic acid, obtained by oxidation with alkaline permanganate melted 121.5° cor., which corresponds to the melting point given by Meldrum and Shah.[50]

The preparation of the corresponding phenylethyl alcohol from 2-methyl-4-brom anisole was not successful. The organo-magnesium halide could not be formed in ether solution. Refluxing for six hours with dry ether, magnesium and iodine as catalyst gave no results. This was repeated several times under varying proportions of solvent but without success. That this may be due to some structural configuration will also be indicated in the preparation of other derivatives from a compound of the same structural type.

In preparing the ether-alcohols without the methyl radicle present the same ortho positions of the alcohol and ether groups had to be kept, else a change in odor could not be strictly accounted for by the removal of the methyl group. Furthermore, according to Cohn[51] isomerism has great influence in the character of odorous substances. In aromatic compounds the ortho substituting group is to be preferred to the para, while meta compounds often lack any odor. So in the removal of the ring-methyl group from β(3-methyl-6-methoxyphenyl)ethanol the most favorable configuration was retained.

An attempt to prepare o-brom phenol directly according to a German patent was unsuccessful.[22] A mixture of the ortho and para compounds was obtained. Therefore this had to be prepared indirectly.

Brombenzene was used as a starting material and was nitrated to obtain o-nitro brombenzene according to the method of Coste and Parry.[23] This was separated from the para compound obtained in the same reaction by extraction with cold methyl alcohol, following the procedure of Dobbie and Marsden.[24] This was then reduced to o-brom aniline, diazotized, hydrolyzed and then methylated. By means of the Grignard reaction with ethylene oxide, β(2-methoxyphenyl)ethanol was obtained. This had a more intensive odor than β(3-methyl-6-methoxyphenyl)ethanol and an agreeable phenolic character.

β(2-ethoxyphenyl)ethanol had been prepared by Stoermer and Kahlert.[26] It was described as having a weak, leek-like odor and boiled 136-7° at 14 mm. Its phenylurethane melted 66°. It was desired to prepare this compound by the same method as used for β(2-methoxyphenyl)ethanol. A second preparation of o-brom phenol from o-nitrobenzene was unsuccessful. So little was obtained that it leads one to suspect that either the reduction did not occur, or else the diazotization did not take place. No check on the physical constants of the o-bromaniline obtained was made. The product obtained had a boiling point of 119° at 21 mm., 123° at 23 mm. and 128° at 37 mm. Since these changes in temperature corresponded to accompanying changes in pressure the substance

was assumed to be pure. In diazotization, however, it was observed that the acid solution gave indication of free nitrous acid on testing with iodo-starch paper after only a small part of the theoretically required sodium nitrate had been added.

To prepare the β(2-ethoxyphenyl)ethanol, for which o-brom phenetole was necessary, two other methods were then tried. Two possibilities were presented. One might start with o-chlor nitrobenzene and prepare o-nitro phenetole according to the method given by Brand,[29] or with o-nitrophenol according to Groll.[2] The former gave a yield of 60% and the latter yields of 55 and 58%. This product was then reduced according to the method of Forster.[6] This gave an impure product boiling over a ten degree range of temperature. By reducing o-nitro phenetole according to the method of Gutekunst and Gray,[49] who prepared p-aminophenyl butyl ether, it was obtained in 65% yield, b.p. 107-117° at 11-12 mm. From this by diazotization in hydrobromic acid solution and subsequent treatment with copper powder one should obtain o-brom phenetole according to Cumming, Hopper and Wheeler.[55] But from 70 grams of o-amino phenetole no o-brom phenetole was obtained.

It was of interest to determine the influence of unsaturation in the alcohol side chain. The odor of γ-phenylpropyl alcohol is materially increased by unsaturation as in cinnamyl alcohol, and it is a question as to whether the odor of the former may not be due to traces of the latter as impurity.[52] This change is not possible with β-phenylethyl alcohol, for phenylvinyl alcohol is unstable, rearranging to phenyl-acetaldehyde. Cinnamyl alcohol types were therefore selected, keeping the same configuration as with the β-phenylethyl alcohol derivatives.

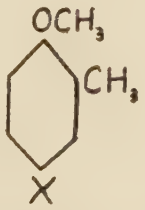
Cinnamyl alcohol has been prepared by the reduction of cinnamaldehyde diacetate and subsequent saponification by Barbier and Leser,[33] by reduction of the aldehyde with iron and acetic acid by Pauly and Schmidt,[53] by reduction with aluminum ethylate by Verley[58] and Meerwein and Schmidt,[59] and by reduction with hydrogen in the presence of platinum black and iron salts by Adams.[60] The advantage of the reduc-

tion with aluminum ethylate and platinum with iron salts was that the carbonyl bond was alone reduced. The older methods gave considerable quantities of phenyl propyl alcohol, which was difficult to separate from cinnamyl alcohol. Since none of the desired cinnamaldehyde derivatives could be prepared, this idea had to be abandoned.

Starting from ortho and para cresol ether an aldehyde was introduced forming 3-methyl-4-methoxy benzaldehyde and 3-methyl-6-methoxy benzaldehyde respectively, according to the method of Gattermann[39] as modified by Adams and Montgomery.[54] The attempt to condense this with acetaldehyde to form the corresponding cinnamaldehyde[12, 14] was unsuccessful.

From these same benzaldehyde derivatives β(3-methyl-4-methoxyphenyl)acrylic acid and β(3-methyl-6-methoxyphenyl) acrylic acid were prepared by condensation with sodium acetate. The yields of the former were very poor. The difficulty in this reaction seemed to be due to the same structural configuration which prevented the formation of a magnesium compound from 2-methyl-4-bromanisole. 3-methyl-4-methoxy benzaldehyde itself was unstable and after standing a few days changed from colorless to a dark red.

Thus it was noticed that in these two examples structure had an inhibiting effect on the entering group. This structure is illustrated by the formula



where X is the group to be replaced. When X was a bromine group the compound did not react with magnesium to form the Grignard reagent. When X was an aldehyde group the condensation with sodium acetate occurred with difficulty.

EXPERIMENTAL

I. The preparation of cresol ethers:

(a) For the preparation of the methyl ethers dimethyl sulphate was used and the method as given by Lassar-Cohn[38] was followed. It was found advantageous to stir the solution during the reaction. It aided in lessening the time of reaction and also increased the yields.

To 1 mol of the cresol dissolved in an excess of 10% sodium hydroxide solution was added by means of a dropping funnel 1.2 mols of dimethyl sulphate, stirring mechanically. This addition took 1½ hours for 94 gr. of the cresol. The temperature was not permitted to exceed 30°. After all had been added the mixture was refluxed for 30 minutes. On cooling the upper layer was separated and washed with cold water. The watery, alkaline solution was extracted once with ether, the ether washed once with water, separated and added to the main product. After drying over anhydrous calcium chloride the solution was filtered and distilled.

(a_1) **p-cresyl methyl ether** was obtained in 90% yield, b.p. 174-76°. Pinette[16] gave the boiling point as 175°.

(a_2) **o-cresyl methyl ether** was obtained in 83% yield, b.p. 169-71°. Pinette[15] gave the boiling point as 171.3°.

(b) In the preparation of the ethyl and butyl ethers the method of Authenrieth and Mühlinghaus[35] was followed. To the p-cresol dissolved in 2 to 3 times its weight of 95% ethyl alcohol, was added one molecular equivalent of metallic sodium cut into small strips. After this had dissolved the alkyl halide was added and the solution heated under reflux for 6 to 7 hours. The solution was then diluted with water, the supernatant layer separated, dried with calcium chloride and distilled.

(b_1) **p-cresyl ethyl ether** was obtained, using ethyl iodide, in 86% yield, b.p. 188-91°. Pinette gave 189.9° as the boiling point, and Authenrieth and Mühlinghaus[35] 187-89°.

(b_2) **p-cresyl butyl ether** was obtained, using n-butyl bromide, in 85% yield, b.p. $_{33-35}$ 129-31°. At normal pressure it distilled 222-26°. Pinette[17] gave 229.5° as the boiling point. Since distillation at atmospheric pressure caused a slight amount of decomposition, a lower pressure was advantageous.

II. The preparation of brom-cresol ethers:

In the bromination of cresol ethers an equal volume of chloroform was used as solvent, a combination of the methods of Claus and Jackson[19] and Meldrum and Shah.[50] This aided in the final separation and washing of the products. The flask containing the ether and solvent was cooled with a water bath, keeping the temperature of the reaction between 25° and 30°. Iron in the form of coarse filings or nails was used as a catalyst. The bromine was added with a dropping funnel and the hydrobromic acid evolved was absorbed in cold water. The time necessary depended upon the amounts of the reagents. For 100 grams of cresol ether addition took 1½ hours. After all the bromine had been added the flask was heated on a water bath, refluxing until no more hydrobromic acid was evolved.

The product, reddish-brown in color, was then poured into 3 to 4 times its volume of cold water, separated, washed twice with 5% sodium hydroxide or sodium carbonate solution and again with water. By this means an almost colorless product was obtained. After drying with calcium chloride the chloroform was distilled off and the residue distilled in vacuo.

(1) **2-brom-4-methyl anisole** was obtained in a yield of 81%, b.p.$_{18}$ 118-20° and b.p.$_{20}$ 124-26°. As determined by the method of Siwoloboff[13] the boiling point was 227.5° at 760 mm. Schall and Dralle[10] gave b.p. 225-27°.

(2) **2-brom-4-methyl phenetole** was obtained in a yield of 81%, b.p.$_{10}$ 120-22°, b.p.$_{753}$ 238.5°. Authenrieth and Mühlinghaus[35] reported a yield of 86% and a boiling point 239-40°.

(3) **2-brom-4-methylphenyl butyl ether,** not previously described, was a colorless, mobile liquid. It was obtained in a

yield of 75%. Distilled three times the final product boiled 164° at 27 to 29 mm.

Anal. calc. for $C_{11}H_{15}O$ Br: Br, 32.88; C, 54.31; H, 6.22.
Found: Br, 33.19; C, 54.29; H, 6.28.

(4) **2-methyl-4-brom anisole** was obtained in a yield of 73%. This product easily crystallized from alcohol in shiny plates, m.p. 68° cor. This was not in agreement with Meldrum and Shah,[50] who gave a melting point of 74°. Contrary to their statement it contained no water of crystallization. To follow their procedure more closely, the product was crystallized from dilute acetic acid before analysis.

Anal. calc. for C_8H_9O Br: Br, 39.76; C, 47.77; H, 4.51.
Found: Br, 39.88; C, 47.35; H, 4.44.

III. The oxidation of brom-cresol ethers:

To further identify these compounds they were oxidized to the corresponding benzoic acids. Oxidation according to Schall and Dralle[10] using chromic acid in glacial acetic acid gave poor results. The use of potassium permanganate in slightly alkaline solution—enough to form the salt of the desired acid—according to Meldrum and Shah [50] and Griffith and Hope[57] gave better results. It was found necessary to add twice the calculated amount of potassium permanganate for a complete oxidation to the acid. The alkaline solution was filtered from the precipitated manganese dioxide and the acid precipitated by acidifying with hydrochloric acid. This was then recrystallized from 30% acetic acid.

The higher ethers, as the ethyl and butyl ethers, gave increasingly poor yields. From 5.0 grams of the former only 0.5 grams of the acid are obtained. From the latter none of the desired benzoic acid was obtained. It seemed that the oxidation attacked the ether group, for the odor of butyric acid could be noted in the product. This would also have accounted for the excess of potassium permanganate necessary for the oxidation. This side reaction was perhaps a function of the length of the ether chain.

(1) **3-brom-4-methoxy benzoic acid** prepared according to Schall and Dralle[10] was obtained in 9% yield, m.p. 218.5° cor., which was in agreement with their product.

(2) **3-brom-6-methoxy benzoic acid** was obtained in a yield of 48%, m.p. 121.5° cor., which agreed with that obtained by Meldrum and Shah.[50]

(3) **3-brom-4-ethoxy bonzoic acid** crystallized in light yellow leaflets from 50% acetic acid by addition of water, m.p. 216.5° cor. This has not been previously described.

Anal. calc. for $C_9H_9O_3Br$: C, 44.08; H, 3.70.
Found: C, 43.86; H, 3.75.

IV. The preparation of β-phenylethyl alcohols:

The general method as given by Altwegg[47] and in a British patent [48] was followed.

A flask fitted with an addition tube was provided with a dropping funnel and a reflux condenser, the end of which held a tube of anhydrous calcium chloride and soda lime. Magnesium turnings were put in and just covered with dry ether, freshly distilled from sodium. A few crystals of iodine were added. To this was added slowly the brom cresol ether. After one or two cubic centimeters had been added, if the reaction did not begin, the flask was warmed until the solvent began to reflux. This was usually effective in starting the reaction; if not, then a trace of freshly prepared ethyl magnesium iodide was added. By one or the other of these means the reaction could be started. When once the reaction was under way more ether was added through the condenser. For 150 grams of brom cresol ether 250 to 300 cc. of anhydrous ether were used. The brom cresol ether was then added fast enough to keep the solvent ether refluxing. After all had been added the mixture was heated on a water bath to complete the reaction. If 150 grams of the brom cresol ether were used, this whole process occupied about 4 hours.

The flask was then cooled with a freezing mixture and ethylene oxide was passed into the ether solution of the organomagnesium compound by warming the container to 25°, at

which it boiled. In practice it was necessary to place the flask of ethylene oxide in a water bath at 25°, for if this was not done the cooling produced by evaporation tended automatically to diminish vaporization and in consequence unnecessarily increased the time of reaction. It was also necessary to use a tube with a wide opening dipping into the ether solution. If this was not done clogging of the tube by the addition product occurred. For this reason a thistle tube was employed, which was so adjusted that it just dipped under the surface. This also decreased the time necessary for the reaction as a greater surface of the solution was presented to absorb the incoming gas. This addition took approximately 2 hours for 150 grams of brom cresol ether used. The product formed a dark, gummy solid.

After slightly more than the theoretically required amount of ethylene oxide had been absorbed dry toluene was added—three mols for one of brom cresol ether—and the ether was distilled. This sometimes required only preliminary heating, as the heat developed in the rearrangement was sufficient to drive off all the ether. Sometimes cooling was necessary.

The flask was again cooled with ice water and the product decomposed by the addition of the required amount of 10% sulphuric acid. The toluene layer was separated, washed once with cold water and dried with anhydrous potassium carbonate or sodium sulphate. This solution was filtered into a Claisen distilling flask and at reduced pressure the toluene was distilled, heating on a water bath. A pressure of 60 to 70 mm. sufficed.

The remainder was distilled using a vacuum oil pump. In distilling the alcohols at low pressures a capillary through which air was drawn was used in the distilling flask to insure even distillation. It was observed that the residues left in the flask were always a dark brown color, and that the distillates had a faint yellow tinge, doubtless caused by a partial decomposition by the oxygen taken in. To avoid this the capillary was connected on the outside with a carbon dioxide generator. The gas was washed with water and concentrated sulphuric acid before passing into the distilling apparatus. Before be-

ginning the heating carbon dioxide was passed in till the air in the apparatus had been displaced. Then the apparatus was evacuated and the rate of flow of the gas adjusted with a screw clip. By this means colorless distillates were obtained and the residues were only faintly colored, showing that oxidation occurred at the temperatures necessary for distillation. Several fractionations were necessary to obtain the pure alcohols.

(1) **β(3-methyl-6-methoxyphenyl)ethanol** was obtained in 36% yield as a thick liquid, which solidified on standing, $b.p._{1.25}$ 120-22°. This can be crystallized from petroleum ether (40-60°). It forms thick colorless needles 1 cm. in length. If crystallized more slowly the crystals are finer but longer. After two crystallizations from petroleum ether and drying in a vacuum dessicator in the presence of sulphuric acid and paraffin it melted 45.5° cor.

Anal. calc. for $C_{10}H_{14}O_2$: C. 72.24; H, 8.49.
Found: C, 71.50; H, 8.25.

(2) **β(3-methyl-6-methoxy-phenylethyl)phenylcarbamate.** This was prepared by the method of Wahlbaum.[25]

In a test tube to 1.0 gram of β(3-methyl-6-methoxyphenyl) ethanol was added 0.75 grams of phenylisocyanate. The mixture warmed slightly. The reaction could be hastened by warming gently over a flame. On cooling a thick liquid remained which solidified on addition of petroleum ether. After a thorough mixing this precipitate was filtered and crystallized twice from 70% ethyl alcohol. It formed short, colorless needles, m.p. 74° cor.

Anal. calc. for $C_{17}H_{19}O_3$ N: C, 71.55; H, 6.71.
Found: C, 71.74; H, 6.39

(3) **β(3-methyl-6-ethoxyphenyl)ethanol** was obtained in 40% yield as a thick liquid, $b.p._{1.4}$ 133-133.5. On cooling with ice it solidified, but became liquid at room temperature. Dissolved in petroleum ether it crystallized when the solvent was evaporated at temperatures below 0°.

Anal. calc. for $C_{11}H_{16}O_2$: C, 73.28; H, 8.95.
Found: C, 73.60; H, 8.95.

(4) **β(3-methyl-6-ethoxy-phenylethyl)αnaphthylcarbamate.** This was prepared according to Bickel and French.[62]

1.7 grams of β(3-methyl-6-ethoxyphenyl)ethanol and 1.7 grams α-naphthylisocyanate were mixed and warmed for a few minutes on a hot plate. On cooling the product solidified. This was extracted once with 100 cc. of ligroine (70-100°) and filtered through a hot water funnel. On cooling it crystallized in fine, colorless needles. It was twice crystallized from 75% ethyl alcohol and then melted 123° cor.

Anal. calc. for $C_{22}H_{23}O_3N$: C, 75.60; H, 6.64.
Found: C, 75.44; H, 6.65.

(5) **β(3-methyl-6-butoxyphenyl)ethanol** was obtained in 37% yield as a thick colorless oil, b.p.$_{1.0}$ 134-36°. This required four fractionations, whereby considerable product was lost. It could not be obtained as a solid.

Anal. calc. for $C_{13}H_{20}O_2$: C, 74.94; H, 9.68.
Found: C, 74.50; H, 9.49.

(6) **β(3-methyl-6-butoxy-phenylethyl)αnaphthylcarbamate.** This was prepared the same as before (IV, 4). It was twice crystallized from ligroine (105-20°) and once from 85% ethyl alcohol, m.p. 97-97.5° cor.

Anal. calc. for $C_{24}H_{27}O_3N$: C, 76.34; H, 7.21.
Found: C, 76.15; H, 7.37.

(7) **β(o-anisyl)ethanol** was obtained as a thick, colorless liquid in 35% yield, b.p.$_{1.0}$ 109-12°.

Anal. calc. for $C_9H_{12}O_2$: C, 71.01; H, 7.95.
Found: C, 70.30; H, 7.98.

(8) **β(2-methoxy-phenylethyl)phenylcarbamate.** This was prepared the same as before (IV, 2). It formed small, colorless crystals melting 72-73° cor.

Anal. calc. for $C_{16}H_{17}O_3N$: C, 70.81; H, 6.32.
Found: C, 71.28; H, 6.61.

V. o-nitro-brombenzene.

This was prepared according to the method of Coste and Parry[23] as modified by Dobbie and Marsden.[24]

The total yield of the para and ortho compounds was 80 to 90%, and of this 35 to 45% was o-nitro-brombenzene, m.p. 36-7°. The melting point of the pure product was given as 42°.[24] Our product was not further purified.

VI. o-bromaniline.

This was prepared according to Fittig and Mager[3] by reduction of o-nitro-brombenzene with tin and hydrochloric acid.

The yields on several preparations were 65 to 85%. On distillation at normal pressure it turned from a light yellow to a deep purple with decomposition, so it was distilled at reduced pressure, b.p.$_{21}$ 119°. Fittig and Mager say that it distills without decomposition and is thus distinguished from p-bromaniline. It is possible that a small amount of p-bromaniline was present. They report the boiling point 229° and also a melting point 31-31.5°.[3] It was not obtained in the solid form.

VII. o-bromphenol.

This was prepared according to Fittig and Mager.[3] The diazonium salt was not separated, but immediately hydrolyzed and steam distilled. The yield was 32%. The product obtained from the ether extract of the steam distillate was not further purified.

VIII. o-bromanisole.

This was prepared according to Lassar-Cohn[38] (see I, a). The yield was 65%, b.p. 220-223°, which agreed with that reported by Wallach and Heusler.[18]

IX. o-nitro-phenetole.

(1) According to Gröll[2] o-nitrophenol in 10% alcoholic potassium hydroxide was heated with ethyl iodide in a sealed tube at 140-60°. This was not done. Instead, the mixture was heated under reflux for 8 hours, and in a second experiment for 22 hours. The yields showed very little difference, being 55% and 58% respectively. It was a yellow liquid, b.p.$_{24}$ 155°. The boiling point at atmospheric pressure could not be obtained due to decomposition. According to Brand[29] it was 267°.

(2) o-nitro-phenetole was prepared a second time using the procedure of Brand.[29] o-nitro-chlorbenzene was heated with dilute alcoholic potassium hydroxide. It was obtained in 60% yield, b.p.$_{22}$ 135-40°.

X. o-phenetidine.

(1) Was first prepared according to Forster.[6] It was obtained in 60% yield, b.p. 235-45°. The same author reported a boiling point 229°.

(2) The method given by Gutekunst and Gray[49] in the preparation of p-aminophenyl butyl ether was followed, except that the solution was steam distilled from the reduction mixture instead of extracting with ether. It boiled 107-17° at 11 to 12 mm.

XI. The preparation of benzaldehyde derivatives:

Gattermann's method [39] as modified by Adams and Montgomery[54] was used.

In this experiment a three-necked Wolff bottle was used. Through one a glass tube was passed connected with a hydrogen chloride generator. The middle neck was fitted with a stirrer with a mercury seal and the third with a reflux condenser.

Dry hydrochloric acid gas was passed into a solution of 30 grams of the cresol ether and 52 grams of zinc cyanide in 150 grams of benzene for 2½ hours, until no more was absorbed, keeping the solution cooled and stirring. Then 45 grams of anhydrous aluminum chloride were added slowly and the mixture heated to 55-60°, continuing the stirring and passing in a slow stream of hydrochloric acid gas. At first, on adding the aluminum chloride, the solution became so solid that it could no longer be stirred. The solid was then broken up with a rod by hand. When this had been done, stirring could be continued without further difficulty. The solution first assumed a green color which slowly became dark red. This heating and stirring was continued for 4 hours and then the mixture was poured into a beaker containing ice and 100 cc. of concentrated hychloric acid, where it separated as an orange or brick-red,

gummy solid. Then enough water was added to make a liter of solution and this was refluxed for ½ hour to decompose the imide chloride to the aldehyde. It was then steam distilled, collecting 2 liters of distillate.

The aldehyde was separated from the water and purified by the formation of the bisulphite addition compound. For the latter a saturated solution of 50 grams of sodium bisulphite was used, through which sulfur dioxide was passed. It crystallized very slowly and in all cases was left standing for 12 hours at least. If the solution was stirred a sticky mass formed, so it seemed best to let it stand and separate out slowly. This was then filtered off, washed with alcohol and ether and decomposed with just enough 10% sodium hydroxide, by heating on the steam bath. This was extracted with ether, dried with calcium chloride, and after distilling off the ether the residue was distilled.

(1) **3-methyl-6-methoxy benzaldehyde** was obtained in 47% yield, b.p. 249-51°. Gattermann gave 250°.[39] Its oxime melted 145-46° cor. Gattermann[41] gave 144-45°.

(2) **3-methyl-4-methoxy benzaldehyde** was obtained in 80% yield, b.p. 253-55°. Gattermann[39] gave 251°. Its oxime melted 72-73° cor. Gattermann gave 68 to 70°,[42] and was evidently dealing with an impure oxime.

XII. The preparation of β-phenylacrylic acids:

These were prepared by condensation of the benzaldehyde derivatives with sodium acetate in the presence of acetic anhydride following the procedure given by Gattermann.[61]

1 mol of aldehyde and 1 mol of fused sodium acetate in 3 mols of acetic anhydride were heated for 8 hours at 180°. While still hot this solution was poured into water, boneblacked and filtered hot. On cooling the β-phenylacrylic acids crystallized. They were further purified by crystallization from water or dilute acetic acid.

(1) **β(3-methyl-6-methoxyphenyl)acrylic** acid was obtained in 42% yield, melting 136-43°. After two crystallizations

from 50% acetic acid it melted 149.5-150.5°. This acid had not been prepared before. It formed small colorless needles.

Anal. calc. for $C_{11}H_{12}O_3$: C, 68.72; H, 6.29.
Found: C, 69.35; H, 6.29.

(2) **β(3-methyl-4-methoxyphenyl)acrylic** acid was obtained in 4% yield. 14 grams of 3-methyl-4-methoxy benzaldehyde were recovered. Recrystallized from 50% acetic acid to constant melting point it formed small colorless needles, m.p. 201° cor.

Anal. calc. for $C_{11}H_{12}O_3$: C, 68.72; H, 6.29.
Found: C, 68.95; H, 6.31.

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